REMARKS

Applicants thank the Examiner for withdrawal of the previous rejections under 35 U.S.C. § 102 based on Young et al. and under § 103 based on Liu et al. Applicants understand the Examiner's lack of comment regarding the previous new matter rejection to be a withdrawal of that rejection; Applicants thank the Examiner for withdrawing the previous new matter rejection. To clarify, the only remaining rejection is the rejection under 35 U.S.C. § 103 based on Young et al. and supporting references.

Claims 42, 45-49, 53-59, and 61 are pending. As disclosed herein, claim 42 is currently amended. Support for newly amended claim 42 can be found in the specification of the instant Application at *e.g.*, claim 46, paragraphs [0007], [0011]. No new matter has been introduced. Applicant respectfully requests reconsideration of the claims in light of the following arguments. The Application is in condition for allowance.

Claim Rejections – 35 U.S.C. § 103

Claims 42, 45-49, 53-59, and 61 were rejected under 35 U.S.C. § 103(a) as unpatentable over Young *et al.* (WO 03/018040) in view of Snodderly et al. (2002; Invest. Ophth vis. Sci.), Grueterich et al. (2002; IDS ref #28) and Tseng (2000; IDS ref #1). Although the Examiner states that all pending claims are rejected under 35 U.S.C. § 103(a), in describing the bases for those rejections, the Examiner makes specific reference only to claims 46, 57, and 58. Applicant assumes that the rational for rejection of the remaining pending claims is found in the Examiner's statements regarding Young and the supporting references.

Young et al.

Applicants traverse Examiner's § 103 rejections over Young and the supporting references for the reasons stated below. The pending claims are allowable over the various asserted combinations of Young et al. and supporting references because neither Young nor any of the other

three references discloses a graft suitable for treatment of retinal disease comprising amniotic membrane and about 16,000 to about 20,000 RPE cells per $4mm^2$ of amniotic membrane.

The Examiner asserts that "Young et al. teach a method and a composite graft... where the composite graft comprising RPE cells grown on a base membrane such as amniotic membrane. (abstract and p. 12 lines 2-14)." On the contrary, Young et al. teaches a graft comprising various *layers* – one being a membrane which "acts as an adherent substrate" for a separate layer of cells. Young at p. 12 lines 2-5; *see also id.* at page 5 lines 6-10; *id.* at abstract ("In particular the composite graft of the invention comprises a layer of connecting cells and a layer of photoreceptors.") Further, Young teaches away from growing the necessary intact layer of cells on the membrane layer that is to be a component of the graft. This is clear from Young's teaching that delivery of pigment epithelial cells as a suspension has not been shown to be beneficial in the treatment of human disease. *Id.* at p. 3. Furthermore, Young specifically teaches that delivery of pigment epithelial cells as a suspension results in uneven distribution and failure to form the necessary intact layer of epithelial cells required for the graft. *Id.* at p. 3 lines 27-29. Thus, not only does Young not explicitly disclose cells grown on the membrane which is to be grafted, one of ordinary skill in the art, understanding the teachings of Young, would not be inclined to attempt growing the cells to be transplanted directly on the membrane that is to be used in the transplant.

Therefore, Young does not render the present invention obvious, in fact it teaches away from Applicants' invention. Contrary to Young's teaching that a composite graft must contain a separate substrate layer and a separate layer of epithelial cells, the invention of the instant Application demonstrates that RPE cells may be successfully seeded and grown on an amniotic membrane. Further, the instant Application discloses that this method leads to a composite graft suitable for treatment of retinal disease comprising amniotic membrane and about 16,000 to about 20,000 RPE cells per $4mm^2$ of amniotic membrane – an unexpected result in view of the teachings of Young.

Young et al. in view of Snodderly et al.

The Examiner concedes that Young does not teach a graft wherein the number of RPE cells is 16,000 – 20,000 per 4 mm^2 of amniotic membrane. However, the Examiner asserts that because

Snodderly et al. disclose that the RPE cell density in the central retina of a Rhesus monkey is about 4000 RPE cells/mm^2 up to 7000 RPE cells/mm^2, "it is considered that the monolayer of RPE cells of Young et al. would have the comparable amount of RPE cells per unit area." With all due respect, the teachings of Snodderly regarding RPE cells in the Rhesus monkey are irrelevant to the invention of the present Application. The claims of the present Application are drawn to use of a composite graft, containing human RPE cells, in the treatment of retinal disease in humans; thus the RPE cell concentration that may or may not be found in a Rhesus monkey is immaterial to the patentability of the present claims. For the sake of clarity, Applicants have amended claim 42 in order to make this point more explicit.

Further, the Examiner has not met his *prima facie* case by providing evidence that a rhesus monkey RPF layer is relevant to the density required for human therapeutic use in a human patient.

Claim 46 was rejected under 35 U.S.C. § 103(a) as unpatentable over Young. Applicants traverse Examiner's § 103 rejection over Young for the same reasons as above. Because the instant application provides for unexpected results over Young, Examiner's § 103 rejection over Young should be withdrawn.

Claims 57 and 58 were rejected under 35 U.S.C. § 103(a) as unpatentable over Young. Applicants traverse Examiner's § 103 rejection over Young for the following reasons. First, Applicants traverse the rejection for the same reasons as above. Because the instant application provides for unexpected results over Young, Examiner's § 103 rejection over Young should be withdrawn. Second, Applicants respectfully disagree with the Examiner assertion that "it would have been obvious to a person of ordinary skill in the art to try excimer laser to trim and/or modify the base membrane suitable for transplantation because the excimer laser ablation technique is well known in the art to cut and reshape a variety of tissues and laser treatment is commonly used for eye diseases as numerously disclosed in Young et al." Young discloses the use of lasers directly on the tissues of the intact eye in order to treat disease of the eye. Young at p. 2. In contrast, the present Application describes the use of excimer laser ablation on the amniotic membrane portion of the graft before insertion into the eye. Furthermore, Young in fact teaches away from the use of lasers in the treatment of disease of the eye as it states that such treatments commonly result in patient

dissatisfaction and lack of long-term resolution of the disease symptoms. Young at p. 2. Therefore, one of skill in the art would not make use of the teachings of Young to achieve the invention of Claims 57 and 58.

Young et al. in view of Grueterich et al.

The Examiner concedes that Young does not teach a denuded amniotic membrane. However, the Examiner asserts that the combination of Young and Grueterich, which teaches the use of a denuded amniotic membrane in culturing limbal epithelial cells, renders claims of the instant Application obvious. Applicants traverse Examiner's § 103 rejection over Young in view of Grueterich for the same reasons as stated above. Because the instant application provides for unexpected results over Young, and those unexpected results are not disclosed in Grueterich, Examiner's § 103 rejection over Young in view of Grueterich should be withdrawn.

Young et al. in view of Tseng

The Examiner concedes that Young does not teach an intact amniotic membrane having both a basement membrane and a stroma, nor does it teach the addition of mesenchymal cells to the stroma of a membrane. However, the Examiner asserts that the combination of Young and Tseng, which teaches that an amniotic membrane may possess a basement membrane and a stroma and that mesenchymal cells may be grown on the stroma of an amniotic membrane, renders claims of the instant Application obvious. Applicants traverse Examiner's § 103 rejection over Young in view of Tseng for the same reasons as stated above. Because the instant application provides for unexpected results over Young, and those unexpected results are not disclosed in Tseng, Examiner's § 103 rejection over Young in view of Tseng should be withdrawn.

Similar to the Examiner's rejection based on Young alone, the Examiner further rejects claims 57 and 58 under 35 U.S.C. § 103(a) as unpatentable over Young in view of Tseng. Applicants traverse Examiner's § 103 rejection over Young in view of Tseng for the same reasons stated above in Applicant's arguments that Claims 57 and 58 are not obvious over Young alone. The Examiner acknowledges that Tseng merely discloses that lasers are used "to cut and reshape variety

of tissues." Tseng does not teach or suggest the use of lasers to modify an amniotic membrane that is part of an ocular graft prior to insertion of that graft into the eye of the patient. Thus, the Examiner's § 103 rejection over Young in view of Tseng should be withdrawn.

CONCLUSION

Applicants submit that this paper fully addresses the Non-Final Office Action mailed May 8, 2009. Applicants respectfully solicit the Examiner to expedite prosecution of this patent application to allowance. Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2306. The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 23-2415 (Docket No. 34157-707.831).

Respectfully submitted,

Date: August 10, 2009 By: _____

Michael J. Hostetler, Ph.D., Esq.
Reg. No. 47,664

650 Page Mill Road
Palo Alto, California 94304-1050
858-350-2306
Customer No. 021971